Notice of Allowability	Application No.	Applicant(s)	
	09/581,528	TAKEDA ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment filed 8/19/05 and the interview summary 9/28/05*.

2. ☒ The allowed claim(s) is/are *1,2,5-9,16,29,30,33-36,41,42 and 51*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 5/3/05
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *9/28/05* .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Deborah Crouch
DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1650

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Chuck Niebylski on September 28, 2005.

1. Please rewrite claims

1. A knockin gene-mutated mouse whose genome comprises a mutant presenilin-1 gene, wherein expression of the mutant presenilin-1 gene results in accumulation of Amyloid β 42 in the brain of said mouse.

2. The gene-mutated mouse according to claim 1, wherein the mouse has a mutant presenilin-I gene which comprises a DNA sequence encoding a presenilin-1 protein in which an amino acid in the amino acid sequence of the presenilin-I protein is substituted with a different amino acid.

5. A knockin gene-mutated mouse whose genome comprises a mutant presenilin-1 gene which comprises a DNA sequence encoding a mutant mouse presenilin-1 protein in which isoleucine at position 213 of a mouse presenilin-1 protein as set forth in SEQ ID NO: 3 is substituted with an amino acid other than isoleucine, wherein expression of the mutant presenilin-1 gene results in accumulation of Amyloid β 42 in the brain of said mouse,

6. A knockin gene-mutated mouse whose genome comprises a mutant presenilin-1 gene which comprises a DNA a sequence encoding a mutant mouse presenilin-1 protein in which isoleucine at position 213 of a mouse presenilin-1 protein as set forth in SEQ ID NO: 3 is substituted with threonine.

wherein expression of the mutant presenilin-1 gene results in accumulation of Amyloid β 42 in the brain of said mouse.

7. The gene-mutated mouse according to claim 1, wherein the mouse genome comprises the mutant presenilin-1 gene wherein a DNA sequence encoding an amino acid at position 213 of a mouse presenilin-1 protein as set forth in SEQ ID NO: 3 is mutated to the following sequence:

5'-TGTGGTCGGGATGATYGCC AVC CACTGGAAAGGCCC-3' (SEQ ID NO: 18)

wherein V represents a base other than T, Y represents T or C, and wherein AVC encode the amino acid at position 213.

8. The gene-mutated mouse according to claim 1, wherein the mouse genome comprises the mutant presenilin-1 gene wherein a DNA sequence encoding an amino acid at position 213 of a mouse presenilin-1 protein as set forth in SEQ ID NO: 3 is mutated to the following sequence:

5'-TGTGGTCGGGATGATYGCC ACC CACTGGAAAGGCCC-3' (SEQ ID NO: 19)

wherein Y represents T or C, and wherein ACC encode the amino acid at position 213.

9. The gene-mutated mouse according to claim 1, wherein the mouse genome comprises the mutant presenilin-1 gene wherein a DNA sequence encoding an amino acid at position 213 of a mouse presenilin-1 protein as set forth in SEQ ID NO: 3 is mutated to the following sequence:

5'-TGTGGTCGGGATGATYGCC NNN CACTGGAAAGGCCC-3' (SEQ ID NO:20)

wherein each N independently represents A, G, T, or C, and NNN represents a codon as triplet bases which encodes an amino acid other than isoleucine, Y represents T or C, and wherein NNN encode the amino acid at position 213.

16. The gene-mutated mouse according to claim 1, wherein the mutant presenilin-1 gene is transferred into a mouse ES cell genome by homologous recombination,

29. An isolated mouse embryo whose genome comprises a DNA sequence represented by the nucleotide sequence:

5'-TGTGGTCGGGATGATYGCC ACC CACTGGAAAGGCCC-3' (SEQ ID NO: 19)

wherein Y represents T or C.

30. An isolated mouse embryo of claim 29 obtained by insertion of a mouse ES cell comprising a DNA sequence represented by the nucleotide sequence:

5'-TGTGGTCGGGATGATYGCC ACC CACTGGAAAGGCCC-3' (SEQ ID NO: 19)

wherein Y represents T or C.

33. A primary cell culture or a subcultured cell obtainable by isolating a cell comprising a mutant presenilin-1 gene from the gene-mutated mouse whose genome comprises a mutant presenilin-1 gene according to claim 1 and culturing said cell by tissue culture, wherein expression of the mutant presenilln-1 gene results in accumulation of Amyloid β 42 in said culture.

34. A method for producing a gene-mutated presenilin-1 mouse, comprising introducing a DNA sequence encoding a presenilin-I mutation into mouse ES cells, permitting the DNA sequence to undergo homologous recombination with the genome of said ES cell, thereby inserting the presenilin-1 mutation into the endogenous presenilin-2 gene, transferring said ES cell comprising the mutant presenilin-1 gene into a mouse embryo transferring the embryo to a female mouse and developing the mouse to term.

35. The method according to claim 34, wherein the gene mutated presernilin-1 mouse is capable of expressing a mutant presenilln-1 protein in which isoleucine at

position 213 of a mouse presenilin-1 protein as set forth in SEQ ID NO: 3 is substituted with an amino acid other than isoleucine.

36. A method for evaluating the therapeutic effect or preventive treatment of a substance on Alzheimer's disease, which comprises:

administering a test substance to a gene-mutated mouse whose genome comprises a mutant presenilln-1 gene according to claim 1, then determining a total amount of amyloid β in the brain (M) and the amount of amyloid β 40 and amyloid β 42 in the brain, then calculating a ratio of amyloid β 42/amyloid β 40 (P);

administering a reference substance to a gene-mutated mouse whose genome comprises a mutant presenilin-1 gene according to claim 1, then determining a total amount of amyloid β in the brain (N) and the amount of amyloid β 40 and amyloid β 42 in the brain, then calculating a ratio of amyloid β 42/amyloid β 40 (Q); and

comparing the value of M to N, or the value of P to Q.

41. The method for evaluation according to claim 36, wherein the comparison is conducted for one or more items selected from the group consisting of survival period of time, exploratory behavior, and migratory behavior.

42. A method for evaluating a medicament for therapeutic and/or preventive treatment of Alzheimer's disease which comprises culturing the primary cell culture comprising a mutant presenilin-1 gene or subcultured cell comprising a mutant presenilin-1 gene according to claim 33 in vitro in the presence of a test compound; and determining the effect of said test compound on Amyloid β 42 formation in the cell culture or in the subcultured cell.

51. A gene-mutated mouse whose genome comprises a mutant presenilin-1 gene which encodes for an 0S-2 type mutation of presenilin-1, wherein expression of the

mutant presenilin-1 gene results in accumulation of Amyloid β 42 in the brain of said mouse.

2. Cancel claims 3-4, 10-15, 17-28, 31-32, 37-40 and 43-50.

3. Amend the title to: -- Knockin Gene-Mutated Mouse Comprising a Mutant Presenilin-1 Gene --.

The following is an examiner's statement of reasons for allowance: OS2-type mutation is defined in the specification at page 25, lines 3-4.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 7:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
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September 30, 2005